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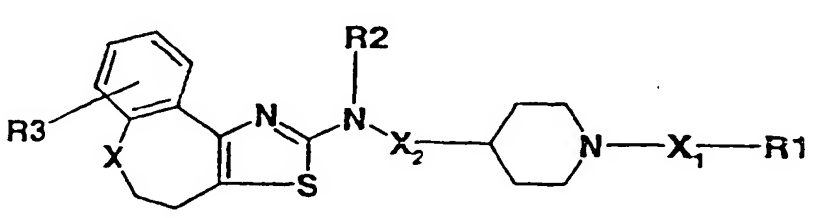

(I)

(57) Abstract: The invention relates to compounds of formula (I) wherein, X is CH_2 or O, X_1 is CO or SO_2 and X_2 is C_1-C_4 alkylene, or a salt, especially a pharmaceutically acceptable salt, thereof. These compounds act against the binding of the neuropeptide Y (NPY) to the Y5-receptor subtype (NPY-antagonism), and might be used in particular for the treatment of adiposity.

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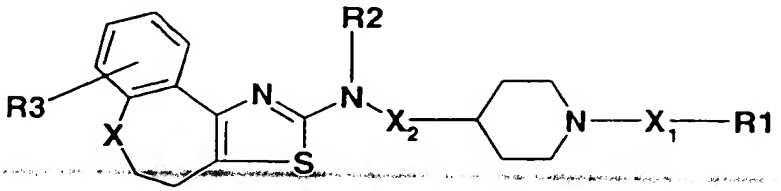
CONDENSED THIAZOLAMINES AND THEIR USE AS NEUROPEPTIDE Y5 ANTAGONISTS

The invention relates to compounds of formula



(I),

wherein

R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, halogen, C_3-C_7-cycloalkyl, phenyl, a monocyclic heterocyclyl radical with one or two hetero atoms selected from O, S or N or by a group of formula -NR4R5; or C_3-C_7-cycloalkyl, phenyl, a monocyclic heterocyclyl radical with one or two hetero atoms selected from O, S or N, or C_1-C_7-alkoxy or C_1-C_7-alkoxy-C_1-C_7-alkoxy;

R2 signifies hydrogen, SO_3H or $P(O)(OH)_2$;

R3 is hydrogen or one or more substituents selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

R4 and R5, independently of one another, signify hydrogen, C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, halogen, trifluoromethyl, a monocyclic heterocyclyl radical with one or two hetero atoms selected from O, S or N or by C_3-C_7-cycloalkyl; or

R4 and R5 together signify C_3-C_7-alkylene or C_4-C_7-alkylene, which is interrupted by O, S or NR6 and which is otherwise either unsubstituted or may be substituted by C_1-C_7-alkoxy; and

R6 signifies hydrogen or C_1-C_7-alkyl;

X signifies CH or O;

X_1 signifies CO or SO_2; and

X_2 signifies C_1-C_4-alkylene;

whereby phenyl and a heterocyclyl radical are respectively unsubstituted or substituted once or more by a substituent selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

or a salt, especially a pharmaceutically acceptable salt, thereof, pharmaceutical preparations containing these compounds, their usage and a method for preparing these compounds.

The compounds of formula (I) may be present especially in the form of pharmaceutically acceptable salts. Acid addition salts may be formed with each basic amino group. The acid component may be, for example, strong inorganic acids, such as mineral acids, e.g. hydrohalic acids, e.g. hydrochloric acid, or strong organic carboxylic acids, e.g. acetic acid or trifluoroacetic acid, or organic sulfonic acids, e.g. methanesulfonic acid or p-toluene-sulfonic acid. In a broader sense, compounds of formula (I) with at least one acid group (for example R2 = SO_3H or $P(O)(OH)_2$) can form salts with bases. Suitable salts with bases are, for example metal salts, such as alkali or alkaline earth metal salts, e.g. sodium, potassium or magnesium salts, or salts with ammonia or an organic amine. In addition, if there is sufficient strength of acid or base, corresponding internal salts may be formed. Also included are salts which are not suitable for therapeutic application, and which may be used for example to isolate or purify free compounds of formula (I) or the pharmaceutically acceptable salts thereof. Only salts that are pharmaceutically acceptable and non-toxic are used therapeutically and those salts are therefore preferred.

If compounds according to the invention have at least two optically active carbon atoms, they may accordingly be present in the form of stereoisomers, stereoisomer mixtures and also in the form of (essentially) pure diastereoisomers. Corresponding compounds with an optically active carbon atom are present as racemates, primarily as (essentially pure) enantiomers. Corresponding stereoisomers are similarly embraced by the present invention.

Unless otherwise defined, the general terms used hereinabove and hereinbelow have the meanings given hereinbelow.

C_1-C_7-alkyl is e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl radical. C_1-C_4-alkyl is preferred, especially methyl.

C_1-C_7-alkoxy is e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy or heptyloxy radical. C_1-C_4-alkoxy is preferred. Methoxy is especially preferred.

Halogen is in particular halogen with an atomic number up to and including 35, i.e. fluorine, chlorine, bromine, and also includes iodine. Chlorine is preferred.

C_3-C_8-cycloalkyl is in particular C_3-C_6-cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Cyclopropyl or cyclohexyl is especially preferred.

A monocyclic heterocyclyl radical with one or two hetero atoms selected from O, S or N may be of aromatic or non-aromatic nature, and is especially 5- or 6-membered. Examples of corresponding heteroaryl radicals are furyl, e.g. 2- or 3-furyl, thienyl, e.g. 2- or 3-thienyl, pyrrolyl, e.g. 1-, 2- or 3-pyrrolyl, 1-C_1-C_7-alkyl-pyrrolyl, e.g. 1-C_1-C_7-alkyl-2- or 1-C_1-C_7-alkyl-3-pyrrolyl, pyrazolyl, e.g. 3- or 4-pyrazolyl, oxazolyl, e.g. 2-, 4- or 5-oxazolyl, e.g. 2-, 4- or 5-oxazolyl, isoxazolyl, e.g. 3- or 4-isoxazolyl, imidazolyl, e.g. 2-, 4- or 5-imidazolyl, thiazolyl, e.g. 2-, 4- or 5-thiazolyl, isothiazolyl, e.g. 3- or 4-isothiazolyl, pyranyl, e.g. 2- or 3-pyranyl, pyridyl, e.g. 2- or 3-pyridyl, pyrazinyl, e.g. 3- or 4-pyrazinyl, pyrimidinyl, e.g. 2- or 4-pyrimidinyl, pyridazinyl, e.g. 2- or 3- pyridazinyl. Corresponding heteroaryl radicals may be partly or wholly hydrogenated. A partly or wholly hydrogenated monocyclic heterocyclyl radical signifies e.g. tetrahydrofuranyl, e.g. 2- or 3- tetrahydrofuranyl, oxo-tetrahydrofuranyl, e.g. 2-oxotetrahydrofuran-3-yl or 3-oxotetrahydrofuran-2-yl, oxo-pyrrolidinyl, e.g. 2-oxo-pyrrolidin-1-yl, 1-C_1-C_7-alkyl-pyrrolidinyl, e.g. 1-C_1-C_7-alkyl-pyrrolidin-2-yl, tetrahydropyrazolyl, e.g. 3-, 4- or 5-tetrahydropyrazolyl, 1-C_1-C_7-alkyl-tetrahydro-pyrazolyl, e.g. 1-C_1-C_7-alkyl-tetrahydropyrazol-3-, -4- or -5-yl, tetrahydrothiazolyl, such as 2-, 4- or 5- tetahydrothiazolyl.

Corresponding aromatic or non-aromatic hetercyclyl radicals are unsubstituted or substituted once or more, e.g. two or three times, by substituents selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro.

C_1-C_7-alkoxy-C_1-C_7-alkoxy is especially C_1-C_4-alkoxy-C_1-C_4-alkoxy, such as methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

C_3-C_7-alkylene is especially 1,3-propylene, 1,4-butylene, 1,5-pentylene or 2,4,-dimethyl-1,5-propylene.

C_4-C_7-alkylene which is interrupted by O, S or NR6, is e.g. C_2-C_3-alkylen-oxy-C_2-C_3-alkylene, such as ethylenoxyethylene or 2-methyl-ethylene-oxy-ethylene, C_2-C_3-alkylene-oxy-C_2-C_3-

alkylene, such as ethylenethioethylene or 2-methyl-ethylene-thio-ethylene, or ethylene-NR_6-ethylene.

C_4-C_7-alkylene substituted by C_1-C_7-alkoxy is for example 1-C_1-C_7-alkoxy-C_4-C_6-alkylene, e.g. 1-methoxymethyl-1,4-butylene.

C_1-C_4-alkylene is especially methylene, but can also signify ethylene, 1,2- or 1,3-propylene, 2-methyl-1,3-propylene or 2,2-dimethyl-1,2-ethylene.

Adiposity is a widespread phenomenon which is responsible for a whole series of illness symptoms and has a negative affect overall on health. It has emerged that eating habits can be regulated by modulating the neuropeptide-Y(NPY)-receptor subtype Y5.

In comprehensive pharmacological studies, it was shown that the compounds of formula (I) and their pharmaceutically acceptable salts have a marked, selective affinity for the receptor subtype Y5 (demonstrated in Y5-binding studies) and have *in vitro* and *in vivo* antagonising properties. These properties are manifested *in vitro* by their ability to inhibit the NPY-induced calcium increase in stably transfected cells which express the Y5-receptor. The antagonistic effect is demonstrated *in vivo* on wake rats by the ability to inhibit food intake induced by intraventricular application of NPY or withdrawal of food for 24 hours. For example, for representative examples of the compounds of formula (I), one hour after administering 30 mg p.o., a reduction in food intake of 57% was established for the compound of example 1, and an inhibition of 25% for the compound of example 7.

The selective affinity for the receptor subtype Y5 may be determined for example using the method described in WO 99/62892. Reference is made in particular to the passages on page 4, paragraph 4, to the end of page 5 of WO 99/62892. The subject matter of this description is incorporated into the present application by reference to this publication.

The compounds according to the present invention may inhibit the food intake induced either by cerebroventricular application of NPY or by withdrawal of food, as well as the spontaneous food intake of adipose Zucker rats and ob/ob mice. These *in vivo* antagonising properties of the compounds according to the invention may be determined, for example, by the methods described in WO 99/62892. Reference is made in particular to

the passages on page 7, paragraph 3, to page 10, paragraph 3, of WO 99/62892. The subject matter of this description is incorporated into the present application by reference to this publication. For example, for representative examples of the compounds of formula (I), an IC_{50} of 6 nM was established for the compound of example 1, an IC_{50} of 7.4 nM for the compound of example 44, and an IC_{50} of 4.6 nM for the compound of example 68.

Accordingly, the compounds (corresponding to the invention as filed) act against the binding of the neuropeptide Y (NPY) to the Y5-receptor subtype (NPY-antagonism), and might be used in particular for the treatment and prevention of disorders or conditions associated with the Y5-receptor subtype, i.e. in which the NPY-Y5-receptor subtype takes part. They may be used preferably for the treatment of illnesses caused by eating disorders, such as adiposity, bulimia nervosa, diabetes, dyslipidemia and hypertension. Moreover, they may be used to treat loss of memory, epileptic convulsions, migraine, sleeping disorders and pain, and in addition, to treat sexual disorders, depression, psychic distress, cerebral bleeding, shock, decompensated cardiac insufficiency, nasal congestion and diarrhoea.

The invention relates to a treatment method of illnesses and disorders associated with the NPY-Y5-receptor subtype, which may be used in particular for the prophylaxis and treatment of disorders and illnesses in which the NPY-Y5-receptor subtype takes part, preferably for the treatment of illnesses caused by eating disorders, such as adiposity, bulimia nervosa, diabetes, dyslipidemia and hypertension. Moreover, they may be used to treat loss of memory, epileptic convulsions, migraine, sleeping disorders and pain, and in addition, to treat sexual disorders, depression, psychic distress, cerebral bleeding, shock, decompensated cardiac insufficiency, nasal congestion and diarrhoea. In this method, warm-blooded animals, including humans, requiring such treatment are given a therapeutically effective amount of a compound of formula (I) or of the pharmaceutically acceptable salt of this compound.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt of this compound, as described above, and as is described in the following for the preparation of a medicament for the prophylaxis and treatment of corresponding illnesses or disorders.

The invention further relates to a medicament which contains a compound of formula (I) or a pharmaceutically acceptable salt of this compound, as described above, and as is described in the following for the treatment of corresponding illnesses or disorders

R1 is preferably C_1-C_4-alkyl, C_1-C_4-alkoxy, tetrahydrofuranyl or halogen-substituted phenyl. R2 is preferably hydrogen. R3 is preferably halogen, such as fluorine or chlorine, or C_1-C_4-alkyl, such as methyl. X_1 is preferably CO. X_2 is preferably methylene.

The invention relates in particular to a compound of formula (I), wherein

R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy or by a group of formula -NR4R5; or C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, a group of formula -NR4R5, C_3-C_7-cycloalkyl, furyl, pyrrolyl, N-C_1-C_7-alkyl-pyrrolyl, thienyl, isoxazolyl, N-C_1-C_7-alkyl-pyrazolyl, N-C_1-C_7-alkyl-pyrrolidinyl, oxopyrrolidinyl, tetrahydrofuranyl, oxo-tetrahydrofuranyl, oxo-thiazolidinyl, thiazolidinyl, phenyl or pyridyl; and

R4 signifies hydrogen or C_1-C_7-alkyl and R5 signifies C_1-C_7-alkyl, C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, C_3-C_7-cycloalkyl, tetrahydrofuranyl or furyl; or C_3-C_7-cycloalkyl or tetrahydrofuranyl; or

R4 and R5 together signify C_3-C_7-alkylene, C_4-C_7-alkylene which is interrupted by O, S or NR6, or C_3-C_7-cycloalkyl; and R6 signifies hydrogen or C_1-C_7-alkyl;

R2 signifies hydrogen;

R3 is hydrogen or one or more substituents selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

X signifies CH or O;

X_1 signifies CO or SO_2; and

X_2 signifies C_1-C_4-alkylene, especially methylene;

whereby phenyl and the heterocyclyl radical are respectively unsubstituted or substituted once or more by a substituent selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

or a salt, especially a pharmaceutically acceptable salt, thereof.

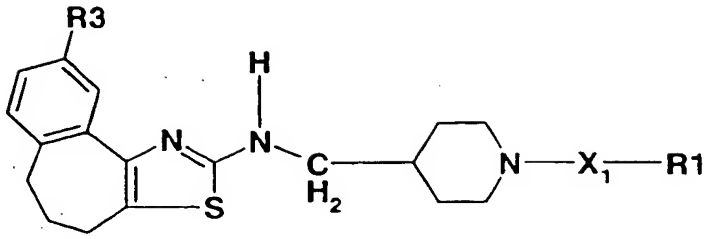
The invention relates in particular to a compound of formula (I), wherein

R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy or by a group of formula -NR4R5; or C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_3-C_7-cycloalkyl, phenyl,

furyl, pyrrolyl, N-C_1-C_7-alkyl-pyrrolyl, thienyl, isoxazolyl, N-C_1-C_7-alkyl-pyrazolyl, N-C_1-C_7-alkyl-pyrrolidinyl, oxopyrrolidinyl, tetrahydrofuranyl, oxo-thiazolidinyl or thiazolidinyl; and
R4 signifies hydrogen or C_1-C_7-alkyl and R5 signifies C_1-C_7-alkyl, C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, C_3-C_7-cycloalkyl, tetrahydrofuranyl or furyl; or C_3-C_7-cycloalkyl; or
R4 and R5 together signify C_3-C_7-alkylene, C_4-C_7-alkylene which is interrupted by O or NR6, or C_3-C_7-cycloalkyl; and R6 signifies hydrogen or C_1-C_7-alkyl;
R2 signifies hydrogen;
R3 is hydrogen or one or more substituents selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;
X signifies CH;
X_1 signifies CO or SO_2; and
X_2 signifies methylene;
whereby phenyl and the heterocyclyl radical are respectively unsubstituted or substituted once or more by a substituent selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;
or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention relates in particular to a compound of formula (I), wherein
R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, halogen, C_3-C_8-cycloalkyl, by amino substituted by C_1-C_7-alkyl and C_3-C_8-cycloalkyl-C_1-C_7-alkyl; or C_1-C_7-alkoxy or tetrahydrofuranyl;
R2 signifies hydrogen;
R3 is C_1-C_7-alkoxy, halogen or trifluoromethyl;
X signifies O;
X_1 signifies CO; and
X_2 signifies methylene;
or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention relates in particular to a compound of formula (IA)



(I A),

wherein

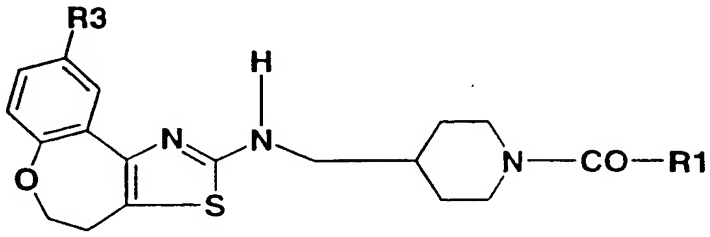
R3 is halogen, such as fluorine or chlorine; or R3 is C_1-C_4-alkyl, such as methyl; and

(i) X_1 is CO and R1 is C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, tetrahydrofuranyl such as 2-tetrahydrofuranyl; or phenyl which is substituted by halogen such as fluorine; or

(ii) X_1 is SO_2 and R_1 is C_1-C_4-alkyl such as methyl;

or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention relates in particular to a compound of formula (IB)



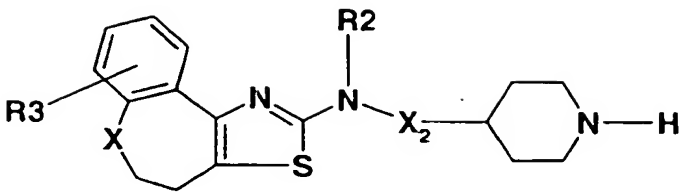
(I B),

wherein

R1 signifies C_1-C_4-alkyl, such as n-butyl, or C_1-C_4-alkoxy-C_1-C_2-alkyl, such as ethoxymethyl; and R3 signifies halogen, such as fluorine; or R3 is C_1-C_4-alkyl, such as methyl; or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention further relates to the compounds according to the invention which are disclosed in the examples.

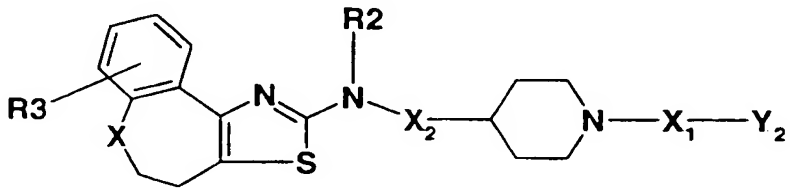
The invention also relates to a method of preparing the compounds according to the invention. A method of preparing a compound of formula (I), is characterised e.g. in that a compound of formula



(II a),

or a salt thereof is reacted with a compound of formula R1-X_1-Y_1 (II a), wherein Y_1 is a leaving group.

A method of preparing a compound of formula (I), wherein R1 signifies C_1-C_7-alkyl, which is substituted by a group of formula -NR4R5 and at least one of radicals R4 and R5 is other than hydrogen, is characterised e.g. in that a compound of formula



(III a),

wherein Y_2 signifies C_1-C_7-alkyl which is substituted by halogen, is reacted with a corresponding amine of formula H-NR4R5 (III b).

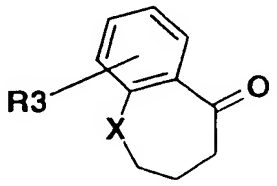
The reactions described hereinbefore and hereinafter are carried out in a known manner, e.g. in the absence or usually in the presence of a suitable solvent or diluent or a mixture thereof, proceeding as required under conditions of cooling, of ambient temperature, or of heating, e.g. in a temperature range of about -80°C to the boiling temperature of the reaction medium, preferably about -10° to about +200°C, and where appropriate in a closed vessel, under pressure, in an inert gas atmosphere, and/or under non-aqueous conditions.

An appropriate leaving group Y_1, which is derived from an activated form of an acid of formula R1-X_1-OH, is primarily halogen, such as chlorine, and also fluorine or bromine.

Halogen in Y_2 signifies chlorine in particular, but may also be bromine or iodine.

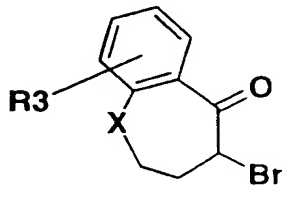
The reaction is preferably carried out in the presence of an organic base. This type of base may be e.g. a tri-C_1-C_7-alkylamine, such as triethylamine, likewise a tri-C_1-C_7-alkylamine with voluminous radicals, e.g. ethyl diisopropylamine, or a heterocyclic base, e.g. pyridine, 4-dimethylaminopyridine or N-methylmorpholine.

The starting material of formula (II a) is prepared, for example, from a compound of formula



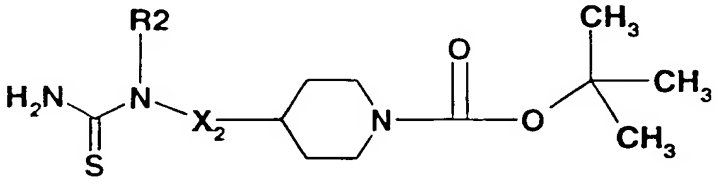
(II c)

which is halogenated, especially brominated, in known manner to form a compound of formula



(II d).

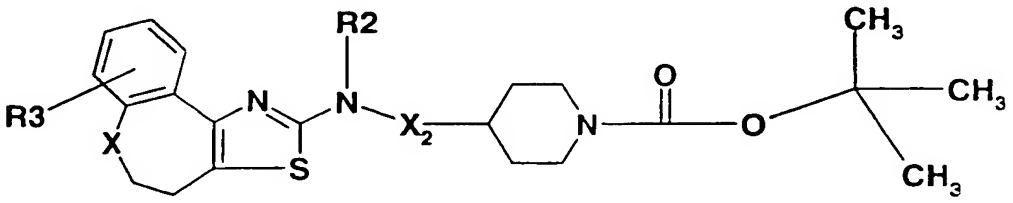
Such a compound of formula (III d) is in turn reacted with a compound of formula



(II e)

in the presence of one of the above-mentioned bases, such as diisopropylethylamine.

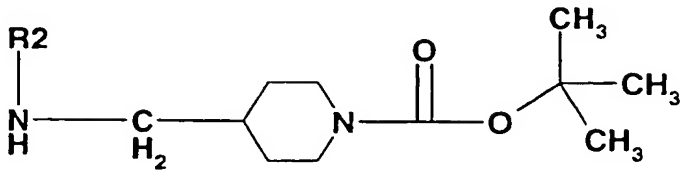
In a compound of formula



(II f),

thus obtained, the amino protecting group is cleaved e.g. by treating with an acid, such as hydrochloric acid, and a corresponding compound of formula (II a) is obtained.

A compound of formula (II e) may be produced e.g. whereby a compound of formula



(II g)

is reacted with phenyl isothiocyanate and the resulting compound is reacted by treating with a base, such as potassium carbonate, to form a compound of formula (II e).

The starting material of formula (III a) may be produced e.g. by reacting a compound of formula (II a) with a compound of formula $Y1\text{-}X_1\text{-}Y_2$ (III c) in the presence of one of the above bases.

The starting material of formulae (II b) and (III b) is partly known or may be prepared in known manner.

The reactions described hereinbefore and hereinafter are carried out in a known manner, e.g. in the absence or usually in the presence of a suitable solvent or diluent or a mixture thereof, proceeding as required under conditions of cooling, of ambient temperature, or of heating, e.g. in a temperature range of about -80°C to the boiling temperature of the reaction medium, preferably about -10° to about +200°C, and where appropriate in a closed vessel, under pressure, in an inert gas atmosphere, and/or under non-aqueous conditions.

The invention is illustrated in particular by the examples and also relates to the new compounds named in the examples and to their usage and to methods for the preparation thereof.

Salts of compounds of formula (I) may be prepared in a known manner. For example, acid addition salts of compounds of formula (I) are obtained by treatment with an acid or in an appropriate ion exchanger reagent. Acid addition salts may be converted into the free compounds in the usual way, e.g. by treatment with an appropriate basic agent.

The acid addition salts obtained may be converted in known manner into other salts, e.g. by treatment with an appropriate metal salt, such as a sodium, barium or silver salt, of another acid in a suitable solvent in which a resulting inorganic salt is insoluble and thus precipitates out from the reaction equilibrium.

The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or may include the solvent used for crystallisation (present as solvates).

Because the new compounds in free form and in the form of their salts are closely related, hereinbefore and hereinafter, the expression free compounds and their salts refers also where appropriate within the meaning and the purpose of this invention to corresponding salts and free compounds.

The diastereoisomer mixtures and enantiomer mixtures obtained may be separated into the pure diastereoisomers and enantiomers in known manner, based on the physical-chemical differences in their components, for example by chromatography and/or fractional crystallisation.

The new compounds of formula (I) may be used e.g. in the form of pharmaceutical preparations, which contain a therapeutically effective amount of the active substance, optionally together with an inorganic or organic, solid or liquid, pharmaceutically acceptable carriers, which are suitable for enteral, e.g. oral, or parenteral administration. The present pharmaceutical preparations which, if so desired, may contain further pharmacologically active substances, are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving or lyophilising processes, and contain from about 0.1% to 100%, especially from about 1% to about 50%, of lyophilisates up to approximately 100% of the active substance.

The invention similarly relates to the usage of the compounds of formula (I), preferably in the preparation of pharmaceutical compositions. Dosaging may depend on various factors, such as mode of application, species, age and/or individual condition. For oral application, the doses to be administered daily are between ca. 0.25 and 300 mg/kg, and for warm-blooded animals with a body weight of ca. 70 kg, preferably between ca. 20 mg and 500 mg.

The invention similarly relates to combinations, e.g. pharmaceutical combinations, containing a compound of formula (I) or (IA) or (IB) or in each case a pharmaceutically acceptable salt thereof, in combination with at least one composition for the treatment of obesity and related conditions and illnesses as listed above, or in each case a pharmaceutically acceptable salt thereof.

Suitable compositions for the treatment of obesity and related conditions and illnesses as listed above are those combined with at least one further active ingredient selected from the group consisting, for example, a NPY receptor antagonist, such as a NPY Y_1, Y_2 and Y_5 receptor antagonist, a combined serotonin and noradrenaline uptake inhibitor, such as sibutramines, a pancreatic lipase inhibitor, such as orlistat, a melanocortin-4-receptor antagonist, an orexin-2 receptor antagonist, a serotonergic active ingredient, such as a 5-HT_{2c}-receptor agonist, and a peripherally active adrenergic active ingredient, such as a β3-adrenoceptor agonist.

The following examples serve to illustrate the invention; the temperatures are indicated in degrees Celsius.

Application Examples Part 1:

General details:

1. Determination of purity or purification by HPLC:

a)

HPLC column dimension: 250 x 3 mm

HPLC column packed with: Nucleosil ® $5C_{18}$

HPLC eluants: A) water + 0.1% by volume of trifluoroacetic acid

A) acetonitrile + 0.1% by volume of trifluoroacetic acid

HPLC gradient X: 20-100% B in 20 minutes + 8 minutes 100%, 0.5 ml/min

HPLC column dimension: 250 x 50 mm - HPLC column packed with: Nucleosil ® $10C_{18}$)

HPLC gradient Y: 20-100% B in 11 minutes +5 minutes 100%, 40 ml/min

b)

HPLC column dimension: 125 x 4 mm

HPLC column packed with: Nucleosil ® 100-5 C_{18}

HPLC eluants: A) water + 0.1% by volume of trifluoroacetic acid

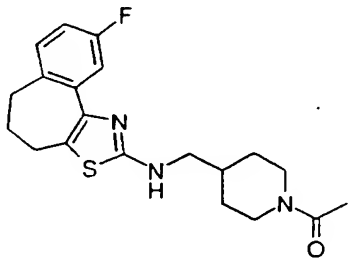
A) acetonitrile + 0.1% by volume of trifluoroacetic acid

HPLC gradient Z: 10-100% B in 5 minutes +2.5 minutes 100%, 1.5 ml/min

2. Analysis of purity using thin-layer chromatography: (solvent systems (LM) used)

A	toluene / ethanol / conc. ammonia	90 : 20 : 1
B	dichloromethane / methanol	19 : 1
C	toluene / ethyl acetate	10 : 1
D	dichloromethane / methanol / conc. ammonia	80 : 8 : 1

Example 1: **1-{4-[(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}-ethanone**



The acetyl chloride is added at 0-5°C to a mixture of (9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine (7.0 g) and diisopropylethylamine (7.17 ml) in dimethylformamide (70 ml). After 15 minutes, the reaction mixture is poured onto ice-water (500 ml) and 10% sodium carbonate solution (50 ml), and the aqueous phase is extracted with ethyl acetate (2 x 200 ml). The combined organic phases are washed with brine, dried over magnesium sulphate and concentrated by evaporation. The title compound, which crystallises upon evaporation, is filtered off and recrystallised from dichloromethane and diethylether. m.p. 161-162° C; Rf = 0.37 (toluene/ethanol/conc. ammonia 90:20:1).

The starting materials may be prepared for example as follows:

4-(3-benzoyl-thioureidomethyl)-piperidine-1-carboxylic acid-tert.-butylester: A solution of benzoyl isothiocyanate (56.1 g) in tetrahydrofuran (100 ml) is added to a solution of 4-aminomethyl-piperidine-1-carboxylic acid-tert.-butyl ester (85 g) [*J. Med. Chem.* 1996, *39*, 487-493] in tetrahydrofuran (500 ml). After 1 hour under reflux, the reaction mixture is concentrated by evaporation and the residue is recrystallised from diethylether and hexane. 4-(3-benzoyl-thioureidomethyl)-piperidine-1-carboxylic acid-tert.-butylester is obtained as white crystals: m.p. 132-133° C; Rf = 0.55 (toluene/ethyl acetate 3:1).

4-thioureidomethyl-piperidine-1-carboxylic acid-tert.-butylester : A solution of 4-(3-benzoyl-thioureidomethyl)-piperidine-1-carboxylic acid-tert.-butylester (196.3 g) in methanol (300 ml) is added to a solution of potassium carbonate (75.9 g) in water (100 ml). After 3 hours under reflux, the reaction mixture is concentrated by evaporation and the residue is mixed with water. The crystalline solid is filtered off and washed with diethylether. 4-thioureidomethyl-piperidine-1-carboxylic acid-tert.-butylester is obtained as white crystals: m.p. 130-131° C; Rf = 0.28 (toluene/ethanol/conc. ammonia 90:20:1).

4-bromo-7-fluoro-3,4-dihydro-2H-benzo[b]oxepin-5-one: A solution of bromine (49.28 g) in dichloromethane (40 ml) is added dropwise at 0-5°C over the course of 10 minutes to a solution of 8-fluoro-1-benzosuberone (50 g) in dichloromethane (850 ml), bromination having set in at 0°C. After stirring for 30 minutes at 0-5°C, the bright yellow reaction solution is poured onto ice-water and extracted with dichloromethane. The combined organic phases are washed with water, aqueous 10% sodium carbonate solution and 3% sodium thiosulfate solution, dried over magnesium sulfate and concentrated by evaporation. 4-bromo-7-fluoro-3,4-dihydro-2H-benzo[b]oxepin-5-one is obtained as a yellowish oil: Rf = 0.32 (toluene).

4-[(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert.-butylester: 4-bromo-7-fluoro-3,4-dihydro-2H-benzo[b]oxepin-5-one (52.7 g, ca. 82%) and diisopropylethylamine (41.2 ml) are added to a suspension of 4-thioureidomethyl-piperidine-1-carboxylic acid tert.-butylester (48.1 g) in ethanol (600 ml). After 5 hours under reflux, the reaction mixture is concentrated by evaporation and the residue dissolved in ice-water (500 ml) and ethyl acetate (300 ml). The aqueous phase is extracted with ethyl acetate, the combined organic phases are washed with 5% aqueous

citric acid solution and 5% sodium carbonate solution, dried over magnesium sulfate and concentrated by evaporation. After recrystallisation from ethyl acetate / hexane, 4-[(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid-tert. butylester is obtained as light bright yellow crystals. m.p. 135-136° C; Rf = 0.47 (toluene/ethyl acetate 3:1).

(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine: 4-[(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert.-butylester (60.7g) is added at 25°C, whilst stirring, to a 5-6 N solution of hydrochloric acid in isopropanol (150 ml). After stirring for 2 hours, 500 ml of tert.-butylmethylether is added and the precipitate is filtered off. After recrystallisation from ethanol / tert.-butylmethylether, the hydrochloride salt is dissolved in methanol (100 ml) and 2N sodium hydroxide solution (400 ml), and the free base is extracted with ethyl acetate. The combined organic phases are washed with brine, dried over magnesium sulphate and concentrated by evaporation. (9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine is obtained as white crystals after crystallisation from ethyl acetate / diethylether: m.p. 170-171° C; Rf = 0.68 (dichlormethane/methanol/water/acetic acid 750:270:50:5).

Example 2: **(9-chloro-5,6-dihydro-4.H.-3-thia-1-aza-benzo[.e.]azulen-2-yl)-(1-methanesulfonyl-piperidin-4-ylmethyl)-amine**

Methanesulfonic acid chloride (0.04 ml) is added at 20°C to a mixture of (9-chloro-5,6-dihydro-4.H.-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine (0.175 g) and pyridine (6.0 ml). The reaction mixture is concentrated by evaporation after 1 hour, and the residue is taken up in ethyl acetate (30 ml), set at pH=4 with 2N hydrochloric acid and washed with water (2x 10 ml), dried over magnesium sulfate and concentrated by evaporation. After purification by chromatography (8 g silica gel, hexane / ethyl acetate / methanol / ammonia 30:30:7:1), the title compound is obtained as a pale beige foam, Rf=0.32 (hexane/ethyl acetate 1:1).

The starting materials may be prepared for example as follows:

4-bromo-7-chloro-3,4-dihydro-2H-benzo[b]ox pin-5-one: Bromine (0.54 ml) is added dropwise at 0-5°C over the course of 5 minutes to a solution of 8-chloro-1-benzosuberone [*J. Chem. Soc. (C)* 1969, 2176-2181] (1.94 g) in ether (20 ml). After stirring for 1 hour at 0-5°C, the reaction solution is poured onto ice-water, the ether phase separated and the aqueous phase extracted with ether. The combined organic phases are washed with 2N sodium hydrogen carbonate solution and water, dried over magnesium sulphate and concentrated by evaporation. 4-bromo-7-chloro-3,4-dihydro-2H-benzo[b]oxepin-5-one is obtained as a yellowish oil: Rf = 0.44 (hexan/ethyl acetate 4:1).

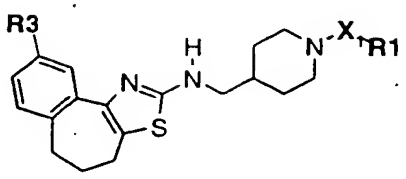
4-[(9-chloro-5,6-dihydro-4.H.-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert.-butylester: Diisopropylethylamine (1.75 ml) is added to a solution of 4-thioureidomethyl-piperidin-1-carboxylic acid tert.-butyl ester (1.400 g) in ethanol (10 ml), and then a solution of 4-bromo-7-chloro-3,4-dihydro-2H-benzo[b]oxepin-5-one (1.365 g,) in ethanol (10 ml) is added. After 4 hours under reflux, the reaction mixture is concentrated by evaporation, and the residue is dissolved in ethyl acetate (50 ml) and extracted with water and brine, dried over magnesium sulfate and concentrated by evaporation. 4-[(9-chloro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert.-butyl ester is obtained as a yellow oil, Rf = 0.64 (dichloromethane/methanol 95:5).

(9-chloro-5,6-dihydro-4.H.-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine: 30% trifluoroacetic acid in dichloromethane (20.0 ml) is added at 0°C, whilst stirring, to a solution of 4-[(9-chloro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert.-butyl ester (2.24g) in dichlormethane (5 ml). After 2.25 hours at 0°C, the mixture is diluted with dichloromethane (40 ml) and rendered alkaline at 0°C with 30% sodium hydroxide solution (15 ml). The mixture is extracted with ether (50 ml). The organic phase is washed with water and brine, dried over magnesium sulfate and concentrated by evaporation. (9-chloro-5,6-dihydro-4.H.-3-thia-1-aza-benzo[.e.]azulen-2-yl)-piperidin-4-ylmethyl-amine is obtained as a foam, Rf=0.05 (dichlormethane/methanol 95:5).

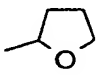
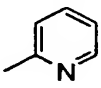
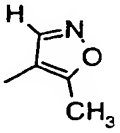
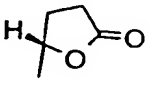
Examples 3 - 38:

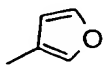
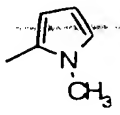
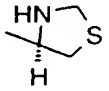
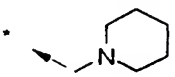
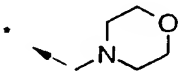
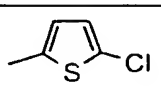
The following may be prepared in analogous manner, for example as described in examples 1 and 2:

Table 1

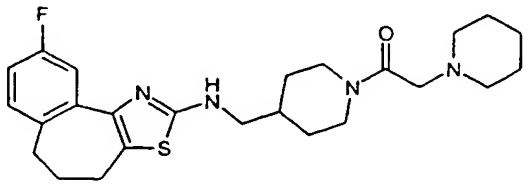


(IC)

No.	X1	R3	R1	m.p. [°C]	Rf (TLC)	TLC elu-ant	Rt (LC)	LC grad.
1	CO	F	CH_3	161-2	0.37	A	12.6	X
2	SO_2	Cl	CH_3				7.8	Z
3	CO	F	$CH(CH_3)_2$	104-5	0.55	A	13.7	X
4	CO	F	CH_2CH_3	155-7	0.42	B	13.6	X
5	CO	F		144-6	0.45	A	12.3	X
6	CO	F	OCH_3	142-4	0.48	A	13.6	X
7	CO	F	OCH_2CH_3	-	0.51	A	14.5	X
8	CO	F	$OC(CH_3)_3$	135-6	0.17	C	16.7	X
9	CO	F	CH_2OCH_3	-	0.37	A	11.5	X
10	CO	F		76-8	0.41	A	12.3	X
11	CO	F		96-8	0.45	A	13.1	X
12	CO	F		200-1	0.27	A	11.6	X

No.	X1	R3	R1	m.p. [°C]	Rf (TLC)	TLC elu-ant	Rt (LC)	LC grad.
13	CO	F		112-3	0.46	A	13.5	X
14	CO	F		-	0.48	B	13.7	X
15	CO	F		102-4	0.44	A	14.4	X
16	CO	F		145-7	0.38	A	9.3	X
17	CO	F		-	0.37	A	11.5	X
18	CO	Cl	o-F-C_6H_4				8.5	Z
19	SO_2	Cl	$N(CH_3)_2$				8.6	Z
20	CO	Cl					6.2	Z
21	SO_2	Cl	CH_2CH_3				8.4	Z
22	SO_2	Cl	$CH_2CH_2CH_2CH_3$				9.2	Z
23	CO	H					4.3	Z
24	CO	Cl	CH_3				7.7	Z
25	CO	Cl	p-F-C_6H_4				9.2	Z
26	CO	F	o-F-C_6H_4				12.0	Z
27	CO	Cl	m-Br-C_6H_4				10.3	Z
28	SO_2	Cl	p-CH_3-C_6H_4				10.1	Z
29	SO_2	Cl					10.7	Z

Example 30: **1-{4-[(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}–2-piperidin-1-yl-ethanone**



A mixture of 2-chloro-1-{4-[(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}-ethanone (815 mg), piperidine (426 mg) and potssium carbonate (414 mg) in dimethylformamide (10 ml) is stirred for 6 hours at 50°C. The mixture is filtered and concentrated by evaporation, and the residue is purified by means of preparative HPLC (250 x 40 mm nucleosil 100-10 C18, gradient Y). The trifluoroacetate salt is converted into the free base with a 10% sodium carbonate solution and extracted with ethyl acetate. By mixing a solution of the free base in ethanol with a 5 N hydrochloric acid solution in isopropanol and subsequently adding diethylether, the dihydrochloride of the title compound is obtained as white crystals. Rf = 0.39 (toluene/ethanol/conc. ammonia 90:20:1).

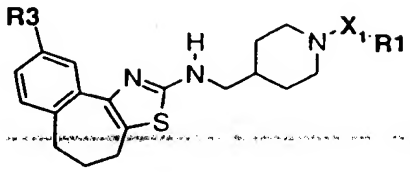
The starting material may be prepared for example as follows:

a) A solution of chloroacetyl chloride (1.11 ml) in dichloromethane (10 ml) is added at 5°C to a mixture of (9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine (4.0 g) and diisopropylethylamine (3.35ml) in dichloromethane (60 ml). After stirring for 15 minutes at 0°C, the reaction mixture is concentrated by evaporation and the residue is partitioned between ethyl acetate and water. The aqueous phase is again extracted with ethyl acetate and the combined organic phases are washed with brine and water, dried over magnesium sulfate and concentrated by evaporation. The title compound is obtained in the form of white crystals by crystallisation from diethylether. m.p. 129-130° C; Rf = 0.54 (toluene/ethanol/conc. ammonia 90:20:1).

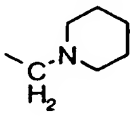
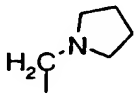
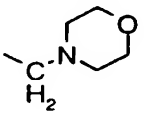
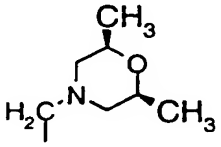
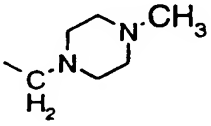
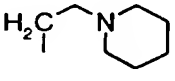
Examples 31 -43:

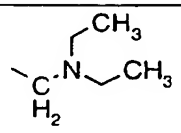
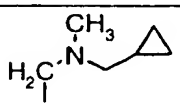
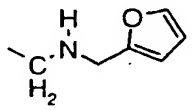
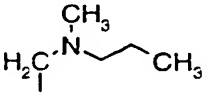
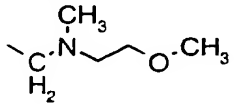
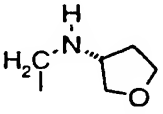
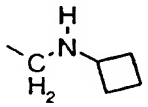
The following may be prepared in analogous manner, for example as described in example 30:

Table 2



(IC)

No.	X1	R3	R1	m.p. [°C]	Rf (TLC)	TLC elu-ant	Rt (LC)	LC grad.
31	CO	F		177-181 di-HCl salt	0.39	A	11.4	X
32	CO	F		- 119-120	0.40	A	11.7	
33	CO	F		- -	0.45	A	11.0	X X
34	CO	F		- 173-182 di-HCl salt	0.6	A	11.7	X X
35	CO	F		178-180 tri-HCl salt	0.24	A	9.2	X
36	CO	F		234-7 di-HCl salt	0.23	A	10.9	X

37	CO	F		150-5 di-TFA salt	0.48	A	10.6	X
38	CO	F		127-130 di-TFA salt	0.49	A	11.1	X
39	CO	F		-	0.39	A	11.6	X
40	CO	F		108-9 di-TFA salt	0.43	A	11.7	X
41	CO	F		-	0.36	A	10.6	X
42	CO	F		104-5	0.45	D	7.7	X
43	CO	F		-	0.50	A	14.7	X

Application Examples Part 2:

General details:

1. Analysis of purity or purification by HPLC:

HPLC column dimension: 250 x 3 mm

HPLC column packed with: Nucleosil ® $5C_{18}$

HPLC eluants:

A) water + 0.1% by volume of trifluoroacetic acid

A) acetonitrile + 0.1% by volume of trifluoroacetic acid

HPLC gradient X: 20-100% B in 20 minutes +8 minutes 100%, 0.5 ml/min

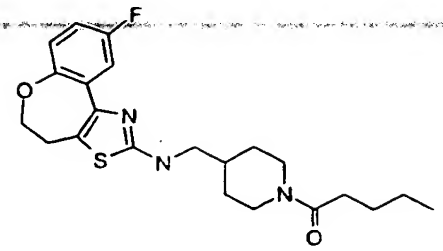
HPLC column dimension: 250 x 50 mm - HPLC column packed with: Nucleosil ® $10C_{18}$)

HPLC gradient Y: 11-100% B in 20 minutes +5 minutes 100%, 40 ml/min

2. Analysis of purity using thin-layer chromatography: (eluant (LM) system employed)

A toluene / ethanol / conc. ammonia 90 : 20 : 1

Example 44: **1-{4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}-pentan-1-one**



A solution of valoryl chloride (2.13 ml) in dichloromethane (10 ml) is added at 0-5°C to a mixture of (9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine hydrochloride (5.5 g) and triethylamine (4.59 ml) in dichloromethane (140 ml). After 30 minutes, the reaction mixture is concentrated by evaporation and the residue is partitioned between ethyl acetate and water. The aqueous phase is again extracted with ethyl acetate and the combined organic phases are washed with 10% sodium carbonate solution and 5% citric acid solution, dried over magnesium sulfate and concentrated by evaporation. The residue is crystallised from diethyl ether. The title compound is obtained in the form of white crystals by mixing a solution of the free base in dichloromethane (50 ml) with a 5 N hydrochloric acid solution in diethylether, and subsequently recrystallising from isopropanol and diethylether in a stoichiometric ratio. m.p. 151-153° C; Rf = 0.37 (toluene/ethanol/conc. ammonia 90:20:1).

The starting materials may be prepared for example as follows:

a) **4-(3-benzoyl-thioureidomethyl)-piperidine-1-carboxylic acid-tert.-butylester:** A solution of benzoyl isothiocyanate (56.1 g) in tetrahydrofuran (100 ml) is added to a solution of 4-aminomethyl-piperidine-1-carboxylic acid-tert.-butyl ester (85 g) [*J. Med. Chem.* **1996**, *39*, 487-493] in tetrahydrofuran (500 ml). After 1 hour under reflux, the reaction mixture is concentrated by evaporation and the residue is recrystallised from

diethylether and hexane. 4-(3-benzoyl-thioureidomethyl)-piperidine-1-carboxylic acid-tert.-butylester is obtained as white crystals: m.p. 132-133° C; Rf = 0.55 (toluene/ethyl acetate 3:1).

b) **4-thioureidomethyl-piperidine-1-carboxylic acid-tert.-butylester** : A solution of 4-(3-benzoyl-thioureidomethyl)-piperidine-1-carboxylic acid-tert.-butylester (196.3 g) in methanol (300 ml) is added to a solution of potassium carbonate (75.9 g) in water (100 ml). After 3 hours under reflux, the reaction mixture is concentrated by evaporation and the residue is mixed with water. The crystalline solid is filtered off and washed with diethylether. 4-thioureidomethyl-piperidine-1-carboxylic acid-tert.-butylester is obtained as white crystals: m.p. 130-131° C; Rf = 0.28 (toluene/ethanol/conc. ammonia 90:20:1).

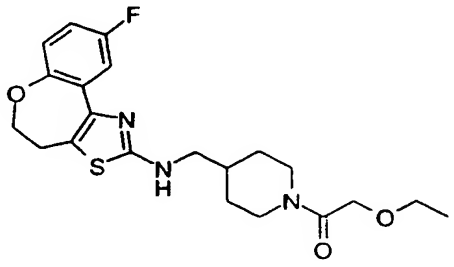
c) **4-bromo-7-fluoro-3,4-dihydro-2H-benzo[b]oxepin-5-one:** A solution of bromine (49.8 g) in dichloromethane (30 ml) is added dropwise at -20°C over the course of 5 minutes to a solution of 7-fluoro-3,4-dihydro-2H-benzo[b]oxepin-5-one (50 g) in dichloromethane (500 ml), bromination having set in at 0°C. After stirring for 15 minutes at 0°C, the bright yellow reaction solution is poured onto ice-water and extracted with dichloromethane. The combined organic phases are washed with water, aqueous 10% sodium carbonate solution and sodium thiosulfate solution, dried over magnesium sulfate and concentrated by evaporation. 4-bromo-7-fluoro-3,4-dihydro-2H-benzo[b]oxepin-5-one is obtained as colourless crystals by crystallisation from hexane: m.p. 56-58° C; Rf = 0.43 (toluene).

d) **4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert.-butylester:** 4-bromo-7-fluoro-3,4-dihydro-2H-benzo[b]oxepin-5-one (50 g) and diisopropylethylamine (47 ml) are added to a suspension of 4-thioureidomethyl-piperidine-1-carboxylic acid tert.-butylester (52.7 g) in ethanol (500 ml). After 1.5 hours under reflux, the reaction mixture is concentrated by evaporation and the residue is mixed with ice-water (1000 ml). After stirring for 2 hours, the crystalline residue is filtered off and washed with diethylether/hexane. After drying in a high vacuum, 4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert. butylester is obtained as light bright

yellow crystals. m.p. 141-143° C; Rf = 0.21 (toluene/ethyl acetate 10:1).

e) **(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine:** 4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert.-butylester (76.4 g) is added at 25°C, whilst stirring, to a 5-6 N solution of hydrochloric acid in isopropanol (150 ml). After stirring for 2 hours, 500 ml of diethylether is added and the precipitate is filtered off. The solid is dissolved in water (200 ml) and mixed with 4N sodium hydroxide solution (85 ml). The free base is extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfat and concentrated by evaporation. (9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine is obtained as beige crystals after crystallisation from ethyl acetate / diethylether. m.p. 157-159° C; Rf = 0.05 (toluene/ethanol/conc. ammonia 90:20:1).

Example 45: **2-ethoxy-1-{4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}-ethanone**



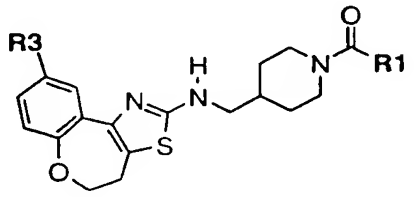
A solution of ethoxy-acetyl chloride (3.04 g) in dichloromethane (10 ml) is added at 0-5°C to a mixture of 2-ethoxy-1-{4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl-amino)-methyl]-piperidin-1-yl}-ethanone hydrochloride (7.3 g) and triethylamine (6.15 ml) in dichlormethane (200 ml). After 10 minutes, the reaction mixture is concentrated by evaporation and the residue is partitioned between ethyl acetate and water. The aqueous phase is again extracted with ethyl acetate and the combined organic phases are washed with 10% sodium carbonate solution, 5% citric acid solution and aqueous 5% sodium bicarbonate solution dried over magnesium sulfate and concentrated by evaporation. The

title compound is crystallised from diethyl ether. m.p. 91-93° C; Rf = 0.39 (toluene/ethanol/conc. ammonia 90:20:1).

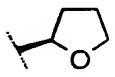
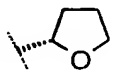
Examples 46 -57:

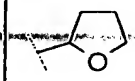
The following may be prepared in analogous manner, for example as described in example 44:

Table 3.

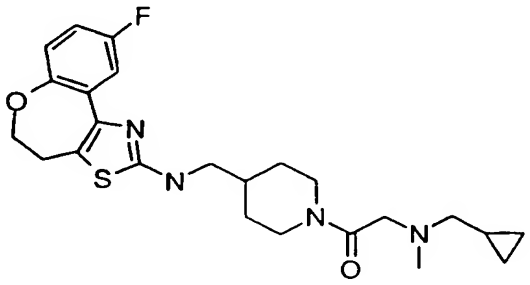


(ID)

No.	R3	R1	m.p. [°C]	Rf TLC	TLC eluant
46	F	$CH_2CH_2CH_2CH_3$	152-4	0.37	A
47	F	$CH_2CH(CH_3)_2$	139-141	0.51	A
48	F	CH_2CH_3	168-170	0.41	A
49	F	CH_3	-	0.45	A
50	F	$CH_2OCH_2CH_3$	91-3	0.39	A
51	F	CH_2OCH_3	137-9	0.42	A
52	F		157-9	0.39	A
53	F		158-160	0.39	A

54	F	OCH_2CH_3	-	0.58	A
55	OCH_3	$CH_2CH_2CH_2CH_3$	127-8	0.37	A
56	OCH_3		-	0.39	A
57	OCH_3			0.38	A

Example 58: **2-(cyclopropylmethyl-methyl-amino)-1-{4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}-ethanone**



A mixture of 2-chloro-1-{4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl-amino)-methyl]-piperidin-1-yl}-ethanone (648 mg), cyclopropylmethyl-methyl-amine (337 mg) and potassium carbonate (314 mg) in dimethylformamide (5 ml) is stirred for 16 hours at 25°C. The mixture is concentrated by evaporation, and the residue is purified by means of preparative HPLC (250 x 40 mm nucleosil 100-10 C18, gradient Y). The trifluoroacetate salt is converted into the free base with a 10% sodium carbonate solution and extracted with ethyl acetate. By mixing a solution of the free base in dichloromethane (5 ml) with a 5 N hydrochloric acid solution in diethylether, the dihydrochloride of the title compound is obtained as an amorphous solid. Rf = 0.45 (toluene/ethanol/conc. ammonia 90:20:1).

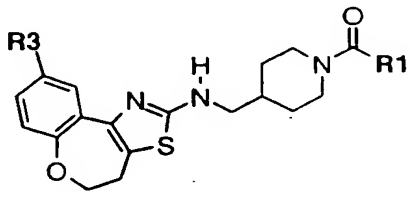
The starting material may be prepared for example as follows:

a) **2-chloro-1-{4-[(9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}-ethanone**: A solution of chloroacetyl chloride (4.05 ml) in dichloromethane (30 ml) is added at 5°C to a mixture of (9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine (15.33 g) and diisopropylethylamine (11.27 ml) in dichloromethane (200 ml). After stirring for 30 minutes at 25°C, the reaction mixture is concentrated by evaporation and the residue is partitioned between ethyl acetate and water. The aqueous phase is again extracted with ethyl acetate and the combined organic phases are washed with brine, dried over magnesium sulfate and concentrated by evaporation. The title compound is obtained in the form of pale beige crystals by crystallisation from diethylether. m.p. 139-141° C; Rf = 0.31 (toluene/ethanol/conc. ammonia 90:20:1).

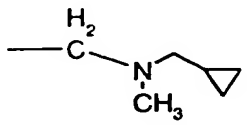
Examples 59 -66:

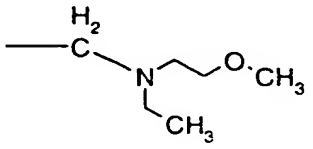
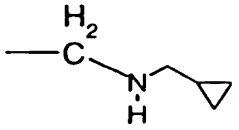
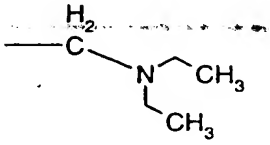
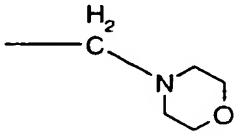
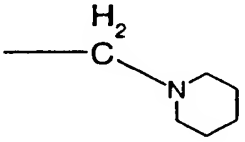
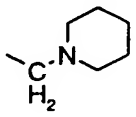
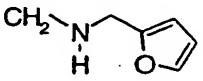
The following may be prepared in analogous manner, for example as described in example 58:

Table 2



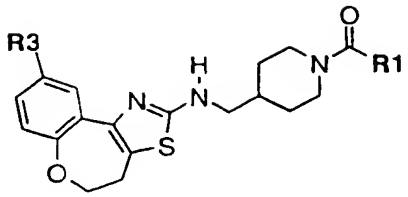
(ID)

No.	R3	R1	Rf TLC	TLC eluant
59	F		0.45	A

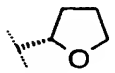
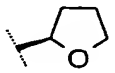
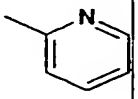
60	F		0.45	A
61	F		0.23	A
62	F		0.45	A
63	F		0.36	A
64	F		0.52	A
65	F		0.41	A
66	F		0.54	A

Example 67:

Compounds 67-71 may be prepared in analogous manner, for example as described in example 1, by using e.g. (9-methyl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[.e.]azulen-2-yl)-piperidin-4-ylmethyl-amine instead of (9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-piperidin-4-ylmethyl-amine. (9-Methyl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[.e.]azulen-2-yl)-piperidin-4-ylmethyl-amine may be prepared by employing the same process conditions as for the preparation of (9-fluoro-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[.e.]azulen-2-yl)-piperidin-4-ylmethyl-amine (see example 1) and using 4-methylphenol instead of 4-fluorophenol as the starting material.



(ID)

No.	R3	R1	m.p. [°C] / $[\alpha]_D^{20}$ [°]	Rf TLC	TLC eluant
67	CH_3	$-CH(CH_3)_2$		R_f =0.5	EtOAc
68	CH_3	 (R)	161-162°C		
89	CH_3	 (S)	$[[\alpha]_D^{20}$ = +17.7° (c = 1, dichloromethane)]		
70	CH_3	$-CH_2-O-C_2H_5$		R_f =0.33	EtOAc
71	CH_3			R_f =0.18	dichloromethane/ methanol = 95 : 5
72	CH_3	$-(CH_2)_3-CH_3$		R_f =0.4	dichloromethane/ methanol = 95 : 5

Formulation example: Hard gelatin capsules containing 100 mg of active ingredient, e.g. 1-{4-[(9-fluoro-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamino)-methyl]-piperidin-1-yl}-ethanone or a salt, e.g. the hydrochloride, thereof, may be prepared e.g. as follows:

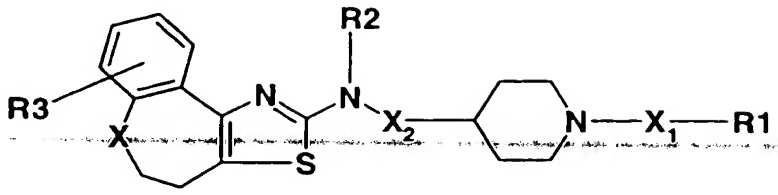
Composition (for 1000 capsules)

active ingredient	100.0 g
lactose	250.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is sifted into the lyophilised active ingredient through a sieve of mesh size 0.2 mm. The two components are mixed thoroughly. Then, first of all the lactose is sifted in through a sieve of mesh size 0.6 mm, followed by the microcrystalline cellulose through a sieve of mesh size 0.9 mm. Subsequently, thorough mixing takes place again for 10 minutes. Finally, the magnesium is sifted in through a sieve of mesh size 0.8 mm. After mixing for a further 3 minutes, 390 mg portions of the obtained formulation are filled into hard gelatin capsules of size 0.

What is claimed is:

1. A compound of formula



(I),

wherein

R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, halogen, C_3-C_7-cycloalkyl, phenyl, a monocyclic heterocyclyl radical with one or two hetero atoms selected from O, S or N or by a group of formula -NR4R5; or C_3-C_7-cycloalkyl, phenyl, a monocyclic heterocyclyl radical with one or two hetero atoms selected from O, S or N, or C_1-C_7-alkoxy or C_1-C_7-alkoxy-C_1-C_7-alkoxy;

R2 signifies hydrogen, SO_3H or $P(O)(OH)_2$;

R3 is hydrogen or one or more substituents selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

R4 and R5, independently of one another, signify hydrogen, C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, halogen, trifluoromethyl, a monocyclic heterocyclyl radical with one or two hetero atoms selected from O, S or N or by C_3-C_7-cycloalkyl; or

R4 and R5 together signify C_3-C_7-alkylene or C_4-C_7-alkylene, which is interrupted by O, S or NR6 and which is otherwise either unsubstituted or may be substituted by C_1-C_7-alkoxy; and

R6 signifies hydrogen or C_1-C_7-alkyl;

X signifies CH or O;

X_1 signifies CO or SO_2; and

X_2 signifies C_1-C_4-alkylene;

whereby phenyl and a heterocyclyl radical are respectively unsubstituted or substituted once or more by a substituent selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

or a salt thereof.

2. Compound according to claim 1, wherein

R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy or by a group of formula -NR4R5; or C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, a group of formula -NR4R5, C_3-C_7-cycloalkyl, furyl, pyrrolyl, N-C_1-C_7-alkyl-pyrrolyl, thienyl, isoxazolyl, N-C_1-C_7-alkyl-pyrazolyl, N-C_1-C_7-alkyl-pyrrolidinyl, oxopyrrolidinyl, tetrahydrofuranyl, oxo-tetrahydrofuranyl, oxo-thiazolidinyl, thiazolidinyl, phenyl or pyridyl; and

R4 signifies hydrogen or C_1-C_7-alkyl and R5 signifies C_1-C_7-alkyl, C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, C_3-C_7-cycloalkyl, tetrahydrofuranyl or furyl; or C_3-C_7-cycloalkyl; or tetrahydrofuranyl; or

R4 and R5 together signify C_3-C_7-alkylene, C_4-C_7-alkylene which is interrupted by O, S or NR6, or C_3-C_7-cycloalkyl; and R6 signifies hydrogen or C_1-C_7-alkyl;

R2 signifies hydrogen;

R3 is hydrogen or one or more substituents selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

X signifies CH or O;

X_1 signifies CO or SO_2; and

X_2 signifies C_1-C_4-alkylene, especially methylene;

whereby phenyl and the heterocyclyl radical are respectively unsubstituted or substituted once or more by a substituent selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

or a salt, especially a pharmaceutically acceptable salt, thereof.

3. A compound of formula (I) according to claim 1, wherein

R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy or by a group of formula -NR4R5; or C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_3-C_7-cycloalkyl, phenyl, furyl, pyrrolyl, N-C_1-C_7-alkyl-pyrrolyl, thienyl, isoxazolyl, N-C_1-C_7-alkyl-pyrazolyl, N-C_1-C_7-alkyl-pyrrolidinyl, oxopyrrolidinyl, tetrahydrofuranyl, oxo-thiazolidinyl or thiazolidinyl; and

R4 signifies hydrogen or C_1-C_7-alkyl and R5 signifies C_1-C_7-alkyl, C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, C_3-C_7-cycloalkyl, tetrahydrofuranyl or furyl; or C_3-C_7-cycloalkyl; or

R4 and R5 together signify C_3-C_7-alkylene, C_4-C_7-alkylene which is interrupted by O or NR6, or C_3-C_7-cycloalkyl; and R6 signifies hydrogen or C_1-C_7-alkyl;

R2 signifies hydrogen;

R3 is hydrogen or one or more substituents selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

X signifies CH;

X_1 signifies CO or SO_2; and

X_2 signifies methylene;

whereby phenyl and the heterocyclyl radical are respectively unsubstituted or substituted once or more by a substituent selected from the group consisting C_1-C_7-alkyl, C_1-C_7-alkoxy, halogen, trifluoromethyl, cyano and nitro;

or a salt, especially a pharmaceutically acceptable salt, thereof.

4. A compound of formula (I) according to claim 1, wherein

R1 signifies C_1-C_7-alkyl or C_1-C_7-alkyl which is substituted by C_1-C_7-alkoxy, halogen, C_3-C_8-cycloalkyl, by amino substituted by C_1-C_7-alkyl and C_3-C_8-cycloalkyl-C_1-C_7-alkyl; or C_1-C_7-alkoxy or tetrahydrofuranyl;

R2 signifies hydrogen;

R3 is C_1-C_7-alkoxy, halogen or trifluoromethyl;

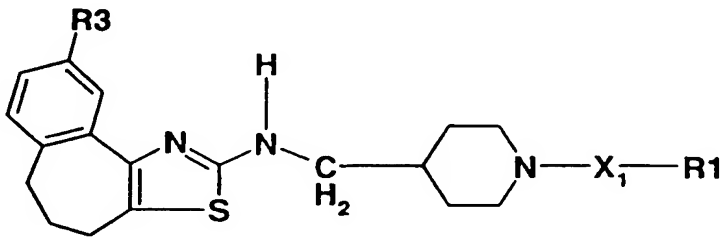
X signifies O;

X_1 signifies CO; and

X_2 signifies methylene;

or a salt, especially a pharmaceutically acceptable salt, thereof.

5. A compound of formula (IA) according to claim 1,



(I A),

wherein

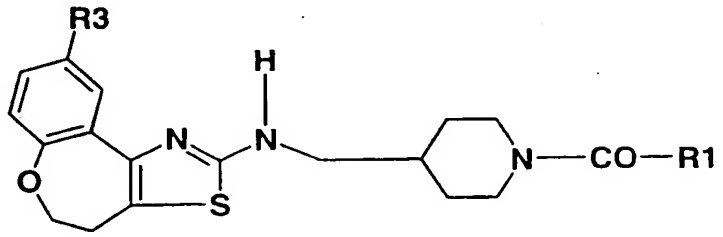
R3 is halogen, such as fluorine or chlorine; or R3 is C_1-C_4-alkyl, such as methyl; and

(i) X_1 is CO and R1 is C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, tetrahydrofuranyl such as 2-tetrahydrofuranyl; or phenyl which is substituted by halogen such as fluorine; or

(ii) X_1 is SO_2 and R_1 is C_1-C_4-alkyl such as methyl;
or a salt, especially a pharmaceutically acceptable salt, thereof.

6. A compound of formula (IA) according to claim 5, wherein R3 is halogen, such as fluorine or chlorine, or C_1-C_4-alkyl, such as methyl;
X_1 is CO and R1 is tetrahydrofuranyl, such as 2-tetrahydrofuranyl;
or a salt, especially a pharmaceutically acceptable salt, thereof.

7. A compound of formula (IB) according to claim 1,



(I B),

wherein
R1 signifies C_1-C_4-alkyl, such as n-butyl, or C_1-C_4-alkoxy-C_1-C_2-alkyl, such as ethoxymethyl; and R3 signifies halogen, such as fluorine; or R3 is C_1-C_4-alkyl, such as methyl; or a salt, especially a pharmaceutically acceptable salt, thereof.

8. Pharmaceutical preparation comprising a compound according to one of claims 1 to 7 and a pharmaceutically acceptable excipient or additive.

9. Pharmaceutical preparation according to claim 8, comprising as a further active ingredient at least one compound selected from the group consisting, for example, a NPY receptor antagonist, such as a NPY Y_1, Y_2 and Y_5 receptor antagonist, a combined serotonin and noradrenaline uptake inhibitor, such as sibutramines, a pancreatic lipase inhibitor, such as orlistate, a melanocortin-4-receptor antagonist, an orexin-2 receptor antagonist, a serotonergic active ingredient, such as a 5-HT_{2c}-receptor agonist, and aperipherally active adrenergic active ingredient, such as a β3-adrenoceptor agonist.

10. Usage of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to one of claims 1 to 7 in the preparation of a medicament for the treatment of adiposity and related diseases.

INTERNATIONAL SEARCH REPORT

Interm. ial Application No
PCT/EP 01/02339

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 C07D417/14 C07D513/04 C07F9/6561 C07F9/6541 A61K31/454 A61K31/662 A61P31/04 //(C07D513/04,313:00, 277:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MCNALLY J J ET AL: "N-(Sulfonamido)alkyl'tetrahydro-1H-benzo'e!indol-2-yl!amines: potent antagonists of human neuropeptide Y Y5 receptor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 10, no. 3, February 2000 (2000-02), pages 213-216, XP004188819 ISSN: 0960-894X the whole document --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2001	11/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/EP 01/02339

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	YOUNGMAN M A ET AL: "Alpha-substituted N-(sulfonamido)alkyl-beta-aminotetralins: potent and selective neuropeptide Y Y5 receptor antagonists" JOURNAL OF MEDICINAL CHEMISTRY,AMERICAN CHEMICAL SOCIETY. WASHINGTON,US, vol. 43, no. 3, 10 February 2000 (2000-02-10), pages 346-350, XP002153193 ISSN: 0022-2623 the whole document	1,8-10
A	WO 99 62892 A (NOVARTIS AG) 9 December 1999 (1999-12-09) cited in the application the whole document	1,8-10
P,X	WO 01 02379 A (SYNAPTIC PHARMACEUTICAL CORPORATION ET AL) 11 January 2001 (2001-01-11) the whole document	1-10
P,Y	WO 00 51602 A (AVENTIS PHARMA DEUTSCHLAND GMBH) 8 September 2000 (2000-09-08) the whole document	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna. al Application No
PCT/EP 01/02339

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WO 9962892 A	09-12-1999	DE 19824175 A	02-12-1999
		AU 4501699 A	20-12-1999
WO 0102379 A	11-01-2001	US 6214853 B	10-04-2001
		US 6222040 B	24-04-2001
		US 6225330 B	01-05-2001
		AU 4369700 A	22-01-2001
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		AU 2670300 A	21-09-2000